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COMMENTARY

Syncope Risk Stratification in the ED: Directions for Future Research

Syncope is a common and vexing chief complaint in emergency departments (EDs). In the United States, there are 740,000 annual events of syncope that lead to an ED visit, resulting in 250,000 admissions[1] and $2.4 billion in yearly hospital costs.[2] Because syncope may be the result of a dangerous condition that has not been revealed by the ED evaluation, patients are often admitted for diagnostic purposes. However, admission is associated with low diagnostic and therapeutic yield,[3,4] and there is no evidence that current practice patterns improve quality-of-life or long-term survival.[5] As a result, there is international interest in improving diagnostic algorithms for syncope, and multiple risk-stratification tools have been published that attempt to identify patients who may be safely discharged.[6–12]

The San Francisco Syncope Rule (SFSR) is perhaps the best known example of these decision aides.[9] The SFSR was rigorously derived and identified five predictors for adverse outcomes after syncope, and absence of these factors was associated with very low risk. Validation by the original investigators reported high sensitivity (98%) and specificity (56%).[13]

In this issue of *AEM,* Tan et al.[14] assess the performance of the SFSR in a Singaporean cohort of 1,250 patients who presented to an ED with syncope. The overall sensitivity and specificity for a 7-day adverse outcome were 94 and 51%, respectively. In a post hoc analysis that excluded patients who had dangerous condition identified during the ED evaluation, the SFSR also exhibited a sensitivity of 94%. Emergency physicians admitted 100% of patients who experienced a serious event; strict application of the SFSR would have reduced admissions by 11% at the cost of discharging 6% of patients who experienced a serious outcome. The authors conclude that the SFSR should supplement, rather than replace, clinical judgment.[14]

These findings are consistent with a large and growing literature in other settings. Validation studies in external cohorts suggested less optimistic performance of the SFSR than originally reported,[15–20] and this overall conclusion was confirmed by a meta-analysis of 18 studies.[21] Performance differences from the original reports may be in part due to differing eligibility criteria and definitions of the SFSR predictors, such as what constitutes an "abnormal" electrocardiogram, but it is unlikely that this body of research can be entirely discounted on methodologic grounds.

As researchers who have studied ED syncope risk stratification, we believe that additional validation studies of the SFSR are unlikely to add much incremental value. None of the published decision aides, including the SFSR, are ready for routine clinical use, but they do provide an important foundation for subsequent work. There are excellent articles on the general approach to developing and validating clinical prediction tools[22,23]; here we offer a set of observations and suggestions specific to syncope risk stratification. We acknowledge that risk stratification is just one facet of clinical management, and this editorial does not address other controversies about the workup of syncope, e.g., optimal duration of hospital and outpatient cardiac monitoring, utility of specific tests, and the protocols for observation and syncope specialty units.

PRINCIPLES FOR FUTURE RISK-STRATIFICATION RESEARCH

1. Standardized data reporting. A major challenge to synthesizing existing studies is the marked variation in defining study eligibility, outcomes, and predictors.[21] For example, the criteria for "syncope" have differed among published studies. To address the problem, a multispecialty international expert panel recently published reporting guidelines for syncope risk-stratification research.[24] Adherence to these guidelines should facilitate future literature review, data pooling, and meta-analysis.
2. Exclude patients with "obvious" serious conditions. Virtually all published risk-stratification studies have included patients who had a serious condition identified during the ED evaluation. From a clinical perspective, risk stratification is unnecessary if a dangerous diagnosis is already known. Inclusion of such patients in risk-stratification studies also biases results toward the identification of "obvious" problems. For example, we found that a low hematocrit was predictive of serious outcomes in a managed care cohort of older adults with syncope; however, when patients with obvious gastrointestinal bleed

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were excluded, hematocrit was no longer associated with adverse events.[25]

3. Use clinically coherent outcome categories. Clinicians desire a prediction instrument that excludes "omni-badness," i.e., any dangerous condition that might be associated with syncope. Unfortunately, the factors that predict cardiac arrhythmia, pulmonary embolism, vertebrobasilar stroke, and occult gastrointestinal bleed are likely to be very different. Lumping together such disparate conditions creates the illusion of completeness; in reality, the resulting decision aid will be best at predicting the most common outcome observed in the study cohort and do a poor job at predicting less common outcomes. Although it may be clinically unwieldy, focusing on coherent outcome classes may result in more valid instruments. For example, there are no existing decision aids to exclude "omni-badness" in patients who complain of chest pain; however, there are well-validated risk-stratification scores for the specific diagnoses of coronary ischemia and pulmonary embolism.
4. Use a uniform outcome time frame. Prior investigators have measured outcomes ranging from 7 days to 1 year after the ED index visit. Using short time frames will detect syncope-related outcomes with high specificity at the cost of sensitivity; conversely, long time frames (e.g., 1 year) may not be relevant for deciding whether to acutely admit a patient and will also capture events that are unrelated to the initial syncope episode. Although the determination of a clinically relevant outcome time frame is admittedly arbitrary, an international expert panel suggested the measurement of 30-day outcomes.[24]
5. Enroll large sample sizes. A major challenge to researchers is the relatively low rate of dangerous events after an unrevealing ED evaluation (~7%).[25] Prior derivation studies included between 30 to 104 patients with serious outcomes, and small sample sizes may contribute to unstable models that do not generalize to other settings. External funding and data pooling from multiple cohorts are likely needed to overcome sample size challenges.
6. Evaluate the role of new tests. The approach to evaluating syncope relies on the triad of careful history taking, a comprehensive physical examination, and a 12-lead electrocardiogram. The published literature has been static in the sense that measured predictors, which match this traditional approach to syncope evaluation, have not changed appreciably in the past 20 years. However, newer tests such as high-sensitivity troponins, natriuretic peptides, and bedside cardiac ultrasound performed by emergency physicians may provide objective and prognostic information about structural heart abnormalities which may not have been available in the past. We encourage the evaluation of such technologies in future research.
7. Generate continuous, rather than binary, assessments of risk. The paradigm of identifying "no-risk" patients has tremendous appeal for emergency physicians, and this approach has been successful in the development of clinical decision aids to exclude some types of traumatic injuries. For syncope, no-risk patients are likely to be young and healthy individuals who have a presumptive vasovagal mechanism; identification of such patients is unlikely to improve practice since they are almost never admitted in the first place. However, we are highly skeptical that a no-risk subgroup can be reliably identified in patients for whom there is currently uncertainty about clinical management—older adults who have a nonzero risk of serious outcomes even in the absence of syncope. Furthermore, a binary approach provides no additional information about patients who are categorized as "non–no risk." Finally, disposition after syncope is no longer a binary decision to admit versus discharge, as observation units may provide a safe alternative for the evaluation of intermediate-risk patients.[26] We believe that information about risk categories (e.g., high, intermediate, low), rather than a binary assessment, will provide actionable information to clinicians.
8. Compare decision aids to existing physician performance. Given the difficulty of identifying the no-risk patient, can a risk stratification instrument ever be useful? We believe that a decision aid that, on average, outperforms existing physician practice would be beneficial. That is, a decision aid does not need to be perfect to be helpful. The ideal situation would be a decision aid that has equivalent or better sensitivity, and better specificity, than provider performance. In reality, there are likely to be tradeoffs between sensitivity and specificity, e.g., a decision aid that substantially reduces admissions at the cost of a few missed outcomes. To complicate things further, decision aid performance will likely be context dependent and may safely reduce admissions in some settings but not in others.[20] Despite these challenges, comparison of a new instrument to existing performance is essential to assess the potential benefit of the decision aid. Cost-effectiveness analyses may be helpful to assess decision aids that improve specificity at the cost of sensitivity.
9. Obtain external funding. Although this is an obvious suggestion to conduct high-quality research, obtaining support for syncope studies is challenging. Syncope is an orphan syndrome that does not "belong" to any single disease- or population-specific funding agency. In addition, development of a clinical decision aid may straddle the boundaries of clinical and health services research, which may further complicate the identification of an appropriate sponsor. Creating study teams with complementing expertise (e.g., emergency medicine, cardiology, neurology, geriatrics, internal medicine, health services research) and cultivating relationships with program officers at multiple agencies may improve the chance of funding success.

CREATING A SYNCOPE RESEARCH COMMUNITY

Despite the considerable international interest in improving the management of syncope,[27–29] research has been fragmented across different specialties, countries, and

medical centers. We briefly describe a grass roots effort by syncope researchers to develop an international forum for idea exchange and study collaboration.

The first international workshop on ED syncope risk stratification is being organized by clinical researchers at the University of Milan and will be held in Gargnano, Italy, in September 2013. This forum will include researchers who have made a substantial contribution to syncope risk stratification in the ED. Sessions will summarize the current state of the risk-stratification literature, identify a consensus on "best practices" supported by existing data, identify the areas of uncertainty where more studies are needed, and develop an infrastructure for future international multicenter studies. We believe that this meeting will build on and improve the principles for future syncope risk-stratification research described in this editorial.

SUMMARY

Despite decades of research, there continues to be uncertainty about how best to risk stratify and evaluate patients who present to an ED with syncope. Existing risk-stratification tools, including the SFSR, are not ready for routine clinical use, but they do provide important lessons. We suggest nine principles for future risk stratification research and are hopeful that increasing international interest and collaboration on this topic will result in novel and improved algorithms of care.

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